Gestational Diabetes Mellitus: Connecting Gaps in Pathophysiology, Diagnosis and Management Strategies

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Abstract

Gestational diabetes mellitus (GDM) has emerged as one of the most common metabolic complications of pregnancy, with an alarming rise in prevalence, especially in South and Southeast Asia. Affecting nearly 16–18% of pregnancies worldwide, it poses significant risks for both maternal and fetal health while perpetuating intergenerational transmission of metabolic disorders. Despite extensive research, fundamental gaps remain in understanding its heterogeneous pathophysiology and in establishing uniform diagnostic and management strategies. GDM arises from complex interactions of genetic predisposition, β-cell dysfunction, placental hormonal imbalance, oxidative stress, and gut microbiota dysbiosis. Yet, controversies in diagnostic criteria, particularly between the Carpenter-Coustan and IADPSG guidelines, continue to hinder early detection and standardisation of care. Conventional management through lifestyle modification and pharmacological therapy provides only partial efficacy and limited long-term protection for offspring. Recent advances highlight precision medicine, nutraceuticals, and microbiome-targeted approaches as promising frontiers for individualised care. In this review, we explore major databases, global epidemiology, mechanistic insights, diagnostic challenges, and therapeutic insights from standard guidelines to enhance outcomes. It underscores the urgent need for population-specific guidelines, integration of molecular biomarkers, and structured postnatal follow-up to shift GDM care from reactive management toward proactive prevention.

Keywords:

Gestational diabetes mellitus, insulin resistance, β-cell dysfunction, diagnosis, precision medicine, maternal health, fetal programming, global burden

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders of pregnancy, which includes severe medical conditions for both the mother's and child's health (1). According to the American Diabetes Association (ADA), in GDM, a glucose intolerance is first observed during the second or third trimester in non-diabetic females (2). Although often brief, its influence extends well afar pregnancy, increasing the risk of instant obstetric complications and long-term metabolic disorders in both mother and child. According to the International Diabetes Federation (IDF), GDM affects approximately 16–18% of pregnancies all around the world, with excessively high rates in South-East Asia (24%) and South Asia (20%) (3). These figures are largely indorsed to genetic proneness, quick urbanisation, and diet habit modification in these regions. Worryingly, more than 90% of hyperglycemia in pregnancy now occurs in low- and middle-income countries (LMICs), where gynaecological facilities and diagnostic resources are often limited. In India, a large multi-site study using the IADPSG criteria stated a prevalence of 19.2%, underlining the urgent need for population-specific diagnostic inceptions with cheap, accessible screening strategies (4).

The root cause of pathophysiological interventions of GDM includes several factors, comprising an interplay between chronic insulin resistance and impaired β-cell function. Basically, in pregnancy affected by GDM, progressive insulin resistance, particularly during the second and third trimesters, is common, which is driven by elevated levels of placental hormones such as human placental lactogen (hPL), estrogen, progesterone, cortisol, and placental growth hormone (5). These changes in hormones interfere with insulin receptor signalling in peripheral tissues, enabling sustained maternal hyperglycemia to facilitate glucose transfer to the fetus. In normal pregnancies, this is counterbalanced by adaptive β-cell hypertrophy and increased insulin secretion. However, in women predisposed to metabolic dysfunction, this adaptation of β-cells fails, leading to maternal hyperglycemia and GDM (6).

GDM is not only a transient disorder of pregnancy but also a phenotypic expression of metabolic dysfunction, which becomes revealed under the physiological stress of pregnancy. This theory is supported by the increasing recognition that GDM shares mechanistic features with type 2 diabetes mellitus (T2DM) (7). It is interesting to note that an increase in gluconeogenesis in the liver, disturbed glucose uptake, and progressive failure of the β-cell are also observed in this condition. Indeed, approximately 80% of GDM cases are considered to

reflect primary type 2-like pathophysiology, with GDM serving as an early marker for the development of T2DM later in life (8). Moreover, novel molecular contributors such as inflammatory cytokines (TNF-α, IL-6), adipokines (leptin, adiponectin), oxidative stress, mitochondrial dysfunction, and gut microbial dysbiosis have recently emerged as critical modulators of insulin signalling and glucose homeostasis in pregnancy. Studies have shown that gut microbiota alterations in GDM are linked to increased intestinal permeability and systemic inflammation, while oxidative stress markers correlate with placental GLUT4 downregulation and β-cell apoptosis, providing deeper mechanistic insights into the maternal-fetal metabolic imbalance (9,10). Despite growing evidence, the heterogeneity in diagnostic criteria across international health systems, particularly the use of IADPSG vs. Carpenter-Coustan or WHO criteria, complicates early detection and consistent risk stratification. The debate between universal versus selective screening remains unresolved, especially in LMICs, where resource allocation and patient adherence are critical factors. Furthermore, although conventional treatment (dietary modification, insulin, or metformin) can mitigate hyperglycemia, these interventions do not address the root metabolic dysfunction, and their long-term safety, especially on fetal outcomes, remains inadequately studied (11).

In this review is we have summarised epidemiological trends, molecular mechanisms, and emerging environmental factors in the pathogenesis of GDM, with a particular focus on intergenerational metabolic programming. Growing evidence suggests that early life exposures such as intrauterine undernutrition (low birth weight) or overnutrition (macrosomia) influence future GDM risk via epigenetic reprogramming of insulin and energy metabolism pathways. These developmental origins of health and disease (DOHaD) highlight the cyclical and heritable nature of GDM and the need for interventions targeting preconception and antenatal windows. By bridging current clinical evidence with emerging molecular research, this review aims to offer a comprehensive perspective on GDM pathogenesis and management, ultimately contributing to improved maternal-fetal outcomes and long-term metabolic health.

2. *Epidemiology and Global Prevalence*

Gestational diabetes mellitus (GDM) has emerged as a growing global public health concern, with its prevalence steadily increasing over the past two decades. According to the latest estimates by the International Diabetes Federation (IDF, 2023), GDM affects approximately 16–18% of pregnancies globally, although this figure varies widely depending on population characteristics, screening strategies, and diagnostic criteria(12). The escalating prevalence of

GDM observed in low- and middle-income countries (LMICs), which now account for more than 90% of all cases of hyperglycemia in pregnancy. This reflects a confluence of factors, including increased urbanisation, adoption of Western dietary patterns, rising maternal age, declining physical activity, and widening disparities in healthcare access and health literacy (13). The South-East Asia region demonstrates the highest burden globally, with prevalence rates exceeding 24%, followed closely by South Asia, including India, Pakistan, Bangladesh, and Nepal, where rates surpass 20% in many urban and semi-urban populations. A recent study in 2025 reported a GDM prevalence of 35-41% in Indian women using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (14). These trends are particularly concerning given the higher susceptibility of Asian women to insulin resistance and β-cell dysfunction, even at lower body mass indices (BMIs), which underscores the inadequacy of relying on conventional Western-based diagnostic thresholds in ethnically diverse populations. The ethnic variation in GDM risk is now well established. Populations of South Asian, Hispanic, Indigenous, African, and Middle Eastern descent demonstrate a significantly higher predisposition to GDM compared to Caucasian women. This is attributable to genetic susceptibility, differences in adipose tissue distribution, and cultural dietary patterns. Moreover, within-country disparities are frequently observed, especially in LMICs, where socioeconomic status profoundly affects both risk and diagnosis. Women from lower socioeconomic backgrounds often have limited access to antenatal care, less nutritional awareness, and fewer opportunities for lifestyle modifications, increasing their vulnerability to GDM. Paradoxically, urbanisation in these regions has also fuelled the intake of calorie-dense, low-nutrient foods among middle-income and affluent populations, further elevating metabolic risk. Seasonal variation is an under-recognised but increasingly reported phenomenon in GDM epidemiology. Some studies have documented higher rates of GDM diagnosis during summer months, potentially due to seasonal differences in diet, physical activity, or hormonal rhythms. Temperature-induced changes in insulin sensitivity and alterations in placental hormone dynamics may also contribute to this variability (15). These findings warrant further research into environmental determinants and their interaction with metabolic pathways during pregnancy. The heterogeneity in diagnostic criteria across global health systems significantly influences the reported prevalence and burden of GDM. While the IADPSG criteria based on data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study are now widely recommended by the World Health Organisation (WHO) and other international bodies, several regions continue to rely on older protocols such as the Carpenter-Coustan, National Diabetes Data Group (NDDG), or modified WHO criteria. The IADPSG recommends a one-

step 75 g oral glucose tolerance test (OGTT) and diagnosis with any one abnormal value, which increases sensitivity but also results in higher diagnosis rates and associated healthcare costs (16). In contrast, two-step approaches or more stringent thresholds may miss cases, particularly in asymptomatic women or those without classic risk factors. This lack of uniformity in diagnostic practice complicates both local clinical decision-making and international comparisons of disease burden. In high-income countries (HICs), despite broader adoption of the IADPSG model, there is ongoing debate over the cost-effectiveness of universal screening versus selective screening based on risk factors. In contrast, LMICs often observe structural and logistical barriers to implementing any form of standardised screening, including limited laboratory infrastructure, delayed antenatal booking, and workforce shortages. Consequently, many women with GDM remain undiagnosed or are diagnosed too late to benefit from timely interventions, which contributes to higher rates of maternal and neonatal complications, including macrosomia, stillbirth, and preeclampsia (17).

3. Risk Factors and Predictive Determinants of GDM

Gestational diabetes mellitus (GDM) arises from a multifactorial interplay between genetic susceptibility, hormonal and metabolic adaptations to pregnancy, and various modifiable and non-modifiable risk factors. Understanding the constellation of determinants that contribute to GDM risk is critical for developing effective screening, prevention, and personalized intervention strategies.

3.1 Modifiable Risk Factors

Among the most prominent modifiable risk factors is maternal overweight and obesity, both before and during pregnancy (18). Elevated body mass index (BMI) is associated with insulin resistance and β-cell stress, which is the main cause of the pathogenesis of GDM. Meta-analyses and population-based cohort studies consistently show that women with a pre-pregnancy BMI ≥30 kg/m² are 3 to 5 times more likely to develop GDM compared to women with normal BMI (19). Furthermore, excessive gestational weight gain, particularly in the first and second trimesters, is independently associated with increased GDM risk, regardless of pre-pregnancy weight, including Physical inactivity (20). Sitting behaviour leads to decreased insulin sensitivity, reduced glucose uptake by skeletal muscle, and impaired lipid metabolism, all of which heighten susceptibility to glucose intolerance. Recent findings highlight that women engaging in regular moderate-intensity physical activity before and during early

pregnancy have a significantly lower risk of developing GDM, suggesting that exercise-induced improvements in insulin sensitivity may offer a protective benefit. Dietary quality and composition play a pivotal role. High consumption of refined carbohydrates, saturated fats, trans fats, and sugar-sweetened beverages has been linked to increased risk of GDM (21). Conversely, diets rich in whole grains, fibre, legumes, vegetables, and omega-3 fatty acids demonstrate a protective effect. Notably, recent studies have implicated processed meats and high-protein animal-based diets in promoting hepatic insulin resistance and β-cell stress via mechanisms involving lipotoxicity and oxidative stress. These findings emphasise the need for comprehensive nutritional counselling as a primary prevention strategy (22).

3.2 Non-Modifiable Risk Factors

Several non-modifiable factors also contribute substantially to GDM occurrence. Advanced maternal age (≥35 years) is a well-established determinant, as increasing age is associated with reduced insulin sensitivity and declining β-cell reserve. With rising maternal age trends globally, this risk factor contributes significantly to the growing GDM burden (23). Traditional activities are another powerful predictor. Women of South Asian, Hispanic, African, Indigenous, and Middle Eastern descent exhibit a higher predisposition to GDM, even at lower BMI thresholds. This may be explained by ethnic differences in visceral adiposity, adipokine profiles, and genetic variants affecting insulin signalling. Such observations underscore the importance of adopting ethnicity-specific screening thresholds and risk assessments (24). Family history of type 2 diabetes mellitus (T2DM) is also associated with increased GDM risk, pointing toward shared genetic and environmental risk factors. Polycystic ovarian syndrome (PCOS) is another important contributor, with women affected by PCOS exhibiting higher rates of insulin resistance, chronic inflammation, and β-cell dysfunction—conditions that are exacerbated during pregnancy and may precipitate GDM (25).

3.3 Nutritional Programming and the Role of Birth Weight

Emerging evidence highlights the significance of early-life nutritional programming in modulating GDM risk, forming the basis of the Developmental Origins of Health and Disease (DOHaD) hypothesis. Both low and high birth weights have been linked to dysregulated metabolic programming, which may predispose individuals to glucose intolerance and insulin resistance later in life. Low birth weight, typically reflecting intrauterine growth restriction and poor maternal nutrition, has been associated with reduced β-cell mass and altered insulin

receptor expression. These individuals may compensate inadequately under metabolic stress during pregnancy, increasing GDM susceptibility (26). On the other hand, macrosomia or high birth weight, often resulting from maternal hyperglycemia or obesity, is linked to fetal overexposure to glucose and insulin. This intrauterine hyperinsulinemia can lead to early-onset adiposity and insulin resistance in the offspring, perpetuating an intergenerational cycle of metabolic dysfunction. These findings suggest that fetal programming of insulin sensitivity and β-cell function may serve as a long-term determinant of maternal metabolic response in future pregnancies. Recent studies employing epigenomic and metabolomic profiling have identified changes in gene expression and methylation patterns in placental and fetal tissues from GDM pregnancies, further supporting this concept (27).

4. Physiology and Pathophysiology of Glucose Metabolism in Pregnancy

Pregnancy imposes a dynamic set of physiological demands on maternal metabolism to ensure adequate energy supply to the growing fetus. Among these, the regulation of glucose homeostasis undergoes one of the most significant transformations (28). These changes involve a finely tuned balance between insulin sensitivity, β-cell adaptation, and placental hormone secretion, which collectively maintain maternal euglycemia while ensuring nutrient delivery to the fetus. In certain women, however, maladaptation in these metabolic processes contributes to gestational diabetes mellitus (GDM), a common complication of pregnancy characterised by impaired glucose tolerance with onset or first recognition during gestation (29).

4.1 Normal Insulin Sensitivity and β-Cell Adaptation During Pregnancy

In early pregnancy, maternal metabolism exhibits an anabolic state characterised by enhanced insulin sensitivity. This facilitates increased storage of glucose and lipids in maternal tissues, particularly in adipose depots, which serve as an energy reservoir for later gestation. During this phase, insulin-mediated glucose uptake by skeletal muscle and adipose tissue is efficient, and hepatic glucose production is restrained. This enables effective nutrient storage without compromising maternal glycemic control. As gestation advances into the second and third trimesters, maternal metabolism undergoes a catabolic transition marked by a progressive decline in insulin sensitivity, primarily to ensure a continuous supply of glucose and other nutrients to the fetus. This physiological insulin resistance is considered an adaptive mechanism to prioritise fetal nutrition (30). Studies employing euglycemic hyperinsulinemic clamps in human pregnancies demonstrate that insulin sensitivity may decline by up to 50–

60% in the late second and third trimesters compared to pre-pregnancy levels. To counterbalance this insulin resistance and maintain maternal euglycemia, pancreatic β-cells undergo compensatory changes, including hyperplasia, hypertrophy, and increased insulin secretion. These adaptations are driven by metabolic cues such as elevated glucose levels and hormonal changes, including rising prolactin and placental lactogen concentrations. In healthy pregnancies, these β-cell responses are adequate to prevent hyperglycemia, and fasting glucose concentrations typically remain within the normal range (31).

4.2 Role of Placental Hormones in Insulin Resistance

A critical determinant of pregnancy-induced insulin resistance is the hormonal milieu generated by the placenta. Placental hormones such as human placental lactogen (hPL), estrogen, progesterone, cortisol, and placental growth hormone (PGH) play key roles in modulating maternal insulin action. These hormones progressively increase during gestation and exert antagonistic effects on insulin signalling. Specifically, hPL and PGH interfere with insulin receptor substrate-1 (IRS-1) activation, reducing phosphatidylinositol 3-kinase (PI3K)/Akt pathway signalling in target tissues such as skeletal muscle and adipose tissue (32). This results in impaired translocation of glucose transporter 4 (GLUT4) to the cell surface, thereby limiting glucose uptake. Additionally, elevated maternal cortisol and progesterone levels enhance hepatic gluconeogenesis, contributing to increased endogenous glucose production and exacerbating insulin resistance. Recent research suggests that the placenta may also influence systemic insulin resistance through exosomal communication. Placental exosomes enriched with miRNAs and inflammatory mediators have been shown to disrupt insulin signalling in maternal tissues, indicating a paracrine regulatory mechanism of metabolic adaptation during pregnancy (33).

4.3 Mechanisms of Compensation in Healthy Pregnancies

To maintain glycemic control in the face of rising insulin resistance, β-cell mass and functional capacity must increase significantly during pregnancy. This expansion is facilitated by hormonal stimuli, including prolactin and serotonin signalling within the pancreas, which promote β-cell proliferation and insulin gene transcription. Glucose-sensing mechanisms within the islets also become more responsive, allowing for rapid and robust insulin secretion in response to postprandial glycemic excursions. Moreover, recent evidence highlights the role of gut-derived incretin hormones, such as glucagon-like peptide-1 (GLP-1), in supporting β-

cell adaptation (34). In healthy pregnancies, GLP-1 secretion is enhanced, contributing to improved insulinotropic effects. However, impaired GLP-1 signalling has been observed in GDM pregnancies, indicating a possible mechanism of β-cell insufficiency. Failure of these adaptive mechanisms—due to genetic predisposition, pre-existing insulin resistance, lipotoxicity, or chronic inflammation—can lead to β-cell dysfunction and inadequate insulin response, ultimately resulting in GDM. Thus, the pathophysiology of GDM is characterised by a mismatch between the degree of insulin resistance and the compensatory capacity of pancreatic β-cells (35).

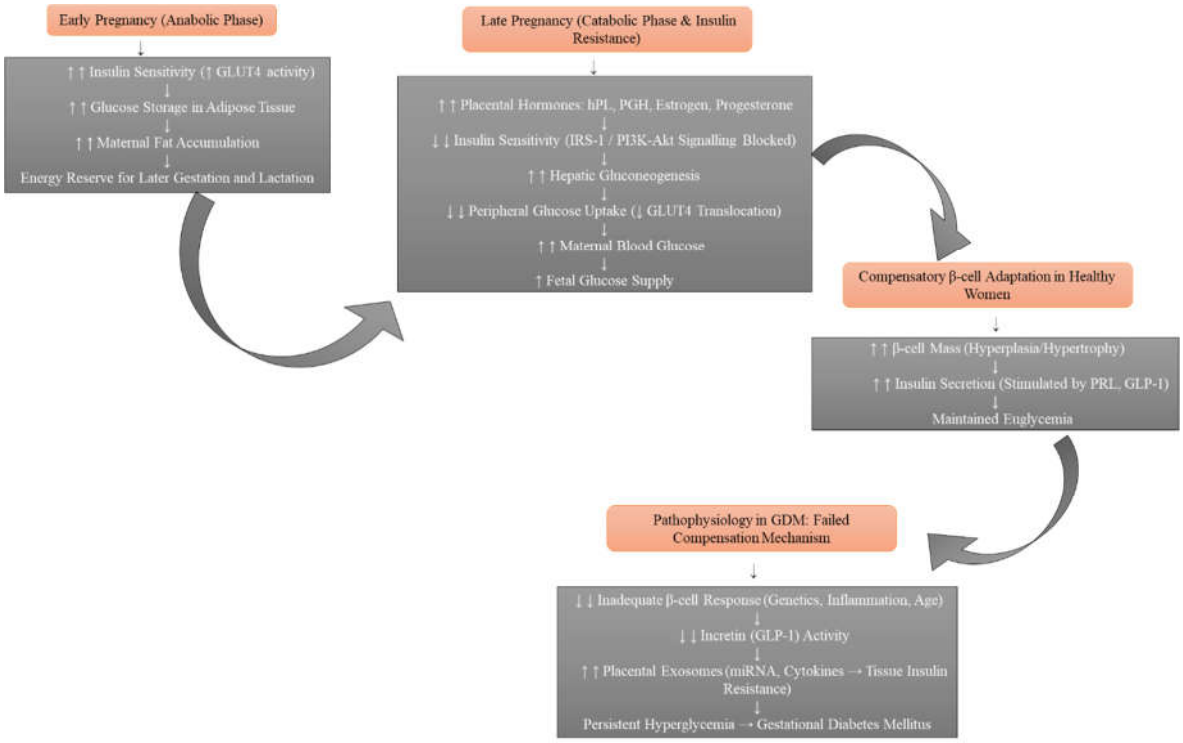

Figure 1: Physiological changes in glucose metabolism during pregnancy and their divergence in gestational diabetes mellitus (GDM). Early pregnancy promotes insulin sensitivity and energy storage, while late pregnancy is characterized by placental hormone-induced insulin resistance. In healthy pregnancies, β-cell adaptation maintains glycaemic control. In GDM, impaired β-cell function and enhanced resistance lead to maternal hyperglycemia.

5. Molecular Pathophysiology of Gestational Diabetes Mellitus (GDM)

Gestational Diabetes Mellitus (GDM) results from a multifactorial disruption of glucose homeostasis during pregnancy, primarily driven by an imbalance between increased insulin resistance and insufficient pancreatic β-cell compensation. While insulin resistance is a normal physiological adaptation of late pregnancy, GDM represents a maladaptive response involving several molecular pathways. Emerging evidence from recent studies (2021–2024) has significantly expanded our understanding of the molecular underpinnings of GDM, implicating

inflammatory signalling, oxidative stress, altered adipokine profiles, placental dysfunction, and gut microbiota alterations as central contributors (36).

5.1 β-Cell Dysfunction and Impaired Insulin Secretion

The foundation of GDM pathophysiology lies in an inability of pancreatic β-cells to adequately compensate for the heightened insulin resistance of pregnancy. In healthy pregnancies, β-cell mass expands through hypertrophy and hyperplasia, accompanied by upregulated insulin synthesis and secretion (37). This is mediated by placental hormones such as human placental lactogen (hPL), prolactin, and estrogen, which enhance insulin gene transcription and β-cell proliferation via pathways involving STAT5, mTOR, and serotonin signalling. In GDM, this adaptive mechanism fails. Studies have demonstrated that β-cell dysfunction in GDM may stem from chronic glucotoxicity, lipotoxicity, and oxidative stress, which impair insulin gene transcription and promote β-cell apoptosis (38,39). Recent research has identified alterations in key transcription factors such as PDX-1, MafA, and NKX6.1 in GDM-affected islets, leading to defective insulin biosynthesis and exocytosis. Moreover, epigenetic modifications, including DNA methylation and miRNA dysregulation (e.g., miR-375, miR-29a), have been shown to impair β-cell function and regeneration in GDM pregnancies (40).

5.2 Placental Hormones and Insulin Resistance

Placental hormones are central to the physiological insulin resistance of pregnancy. These include hPL, placental growth hormone (PGH), progesterone, cortisol, and estrogen. They interfere with insulin receptor substrate-1 (IRS-1) and PI3K-Akt signalling in skeletal muscle and adipose tissue, thereby reducing GLUT4 translocation to the cell membrane and inhibiting glucose uptake. In GDM, this insulin resistance is exaggerated. A 2023 study by Meng et al. demonstrated that GDM placentas exhibit significantly reduced expression of IRS-1 and Akt, along with elevated serine phosphorylation of IRS-1, which impairs downstream insulin signalling. These disruptions are further amplified by placental inflammatory cytokines and hypoxia-induced oxidative stress, both of which promote systemic metabolic dysfunction. Additionally, the JAK/STAT pathway—typically activated by prolactin and hPL to support β-cell expansion—is downregulated in GDM, indicating both central and peripheral disruptions in insulin-regulatory hormonal signalling (37,38).

5.3 *Adipokines and Inflammatory Cytokines*

Adipose tissue plays a critical endocrine role during pregnancy. In GDM, altered secretion of adipokines such as leptin, adiponectin, and resistin contributes to systemic insulin resistance. Leptin levels are elevated in GDM, promoting inflammatory signalling via JNK and NF-κB pathways, while adiponectin—a known insulin sensitiser—is reduced, impairing AMPK activation and enhancing hepatic gluconeogenesis (41,42). Chronic low-grade inflammation is a hallmark of GDM. Elevated levels of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) have been observed in both maternal circulation and placental tissue. TNF-α, in particular, inhibits insulin signalling by inducing serine phosphorylation of IRS-1 and downregulating GLUT4 expression in muscle and adipose tissue. These cytokines also disrupt β-cell survival through increased endoplasmic reticulum (ER) stress and apoptosis (43).

5.4 *Oxidative Stress and Mitochondrial Dysfunction*

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and antioxidant capacity, plays a key role in the development of GDM. Pregnancy itself is a state of increased oxidative demand, but in GDM, this is exacerbated by hyperglycemia and lipotoxicity. ROS impair insulin receptor signalling, activate stress kinases (e.g., JNK, p38 MAPK), and damage mitochondrial DNA (44). Recent studies have shown that placental tissues from GDM pregnancies exhibit increased lipid peroxidation (e.g., MDA levels), reduced antioxidant enzyme activity (e.g., SOD, glutathione peroxidase), and mitochondrial fragmentation. This mitochondrial dysfunction disrupts ATP production necessary for insulin secretion and contributes to β-cell failure (45).

5.5 Gut Microbiota and Metabolic Endotoxemia

An emerging area of interest is the role of the gut microbiota in GDM pathophysiology. Alterations in the composition and diversity of intestinal microbes can influence systemic metabolism via mechanisms involving short-chain fatty acids (SCFAs), bile acid metabolism, and gut barrier integrity. GDM has been associated with reduced abundance of butyrate-producing bacteria (e.g., Faecalibacterium prausnitzii) and increased levels of pathogenic Gram-negative bacteria, leading to elevated circulating lipopolysaccharide (LPS) (46). This metabolic endotoxemia activates TLR4 signalling, promoting systemic inflammation and insulin resistance. Moreover, altered microbial metabolites can impair GLP-1 secretion and modulate hepatic glucose output. Interventional studies using probiotics and prebiotics have

shown modest benefits in glycemic control, although further large-scale trials are warranted (47).

5.6 Epigenetic and Transgenerational Influences

Epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNAs have emerged as mediators of GDM susceptibility. Offspring born to GDM mothers exhibit altered methylation patterns in genes regulating glucose and lipid metabolism, including IGF2, LEP, and PPARγ (48). These changes may predispose the child to insulin resistance, obesity, and early-onset type 2 diabetes, perpetuating an intergenerational cycle of metabolic disease. Maternal hyperglycemia and inflammation during pregnancy are thought to imprint these changes during critical periods of fetal development. Studies using placental and cord blood samples have validated several epigenetic biomarkers that may serve as early indicators of GDM risk and long-term metabolic outcomes (49).

Table 1: Molecular Mechanisms Involved in the Pathophysiology of Gestational Diabetes Mellitus (GDM)

Mechanism	Pathological Effect	Molecular/Cellular Targets	Key Findings	References
β-Cell Dysfunction	Impaired insulin secretion and β-cell apoptosis	PDX-1, MafA, NKX6.1, miR-375, GCK	Chronic glucotoxicity reduces insulin gene expression; β-cell mass fails to expand during pregnancy.	(50)
		miR-29a, miR-223	miRNAs regulate insulin gene transcription and β-cell proliferation	(51)
Placental Hormonal Effects	Pregnancy-induced insulin resistance	hPL, PGH, Estrogen, Progesterone, IRS-1, PI3K-Akt	hPL and estrogen downregulate insulin receptor signalling in maternal muscle and adipose tissue	(52)
Adipokine Imbalance	Increased insulin resistance and systemic inflammation	↑Leptin, ↓Adiponectin, ↑Resistin	Leptin activates pro-inflammatory NF-κB; adiponectin has insulin-sensitising and anti-	(53)

			inflammatory effects.	
Chronic Low-Grade Inflammation	IRS-1 inhibition and β-cell stress	TNF-α, IL-6, CRP	TNF-α impairs insulin signalling via serine phosphorylation of IRS-1; increases ER stress in β-cells	(54)
Oxidative Stress	β-cell apoptosis and impaired insulin signalling	ROS, MDA, SOD, GSH-Px, NOX4	Elevated ROS levels reduce insulin sensitivity and promote apoptosis via mitochondrial damage.	(55)
Mitochondrial Dysfunction	Impaired ATP production and β-cell failure	UCP2, Complex I–IV proteins, SIRT3	Decreased mitochondrial function reduces insulin granule exocytosis; increased mitochondrial fission.	(55,56)
Gut Microbiota Dysbiosis	Increased gut permeability, systemic inflammation, and altered glucose metabolism	↓Faecalibacterium, ↑LPS, ↓GLP-1, SCFA	Dysbiosis increases endotoxemia via LPS; reduced butyrate production impairs glucose homeostasis.	(57)
Incretin Dysfunction	Reduced postprandial insulin response	GLP-1, GIP, DPP-4	Decreased GLP-1 secretion and receptor sensitivity; DPP-4 upregulation reduces incretin half-life.	(58)
Epigenetic Programming	Offspring metabolic risk and altered gene expression	DNA methylation (IGF2, LEP), Histone acetylation, miRNAs	GDM-exposed offspring show altered methylation of genes involved in β-cell function and insulin sensitivity	(49)

6. Current Diagnostic and Therapeutic Strategies for Gestational Diabetes Mellitus (GDM): Challenges and Future Directions

Gestational Diabetes Mellitus (GDM) has emerged as a critical global health concern due to its dual burden on maternal and fetal health (59). With prevalence rates exceeding 16% globally and as high as 24% in certain Asian populations (60), GDM is no longer a condition confined to high-risk groups but has become an increasingly common complication of pregnancy in all around the world. Despite considerable progress in understanding GDM's metabolic basis and its immediate and long-term risks, significant challenges remain regarding timely diagnosis, effective treatment, and prevention of progression to type 2 diabetes mellitus (T2DM) in both mother and child. This section outlines the current diagnostic criteria, treatment modalities, their limitations, and emerging strategies aiming to transform GDM care into a more personalised and effective clinical approach.

6.1. Diagnostic Landscape and Challenges

GDM diagnosis varies globally, resulting in inconsistencies in prevalence estimates and treatment thresholds. The most widely adopted criteria are those proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), based on data from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. These recommendations suggest a one-step 75-gram oral glucose tolerance test (OGTT) between 24–28 weeks of gestation, with diagnosis established if any of the following thresholds are met: fasting plasma glucose ≥92 mg/dL, 1-hour glucose ≥180 mg/dL, or 2-hour glucose ≥153 mg/dL (16). These criteria have demonstrated high sensitivity in detecting maternal hyperglycemia and adverse neonatal outcomes. However, implementation has led to a significant increase in GDM prevalence, raising concerns regarding overtreatment, resource allocation, and increased maternal anxiety (61).

Alternatives include the two-step approach initial 50-gram glucose challenge test (GCT) followed by a 100-gram OGTT for confirmation. This method is still used in the United States and other regions, despite evidence showing it may miss nearly 20% of cases that would be diagnosed under IADPSG guidelines (62). In low- and middle-income countries (LMICs), widespread implementation of the IADPSG criteria remains constrained by limited resources, late antenatal registration, and poor laboratory access. The Diabetes in Pregnancy Study Group India (DIPSI) recommends a simplified, non-fasting 75-gram glucose challenge test for its

feasibility in community settings. However, concerns about lower diagnostic accuracy persist, underlining the tension between practicality and precision in GDM screening.

6.2. Therapeutic Approaches: Current Standards of Care

The primary goal of GDM management is to maintain euglycemia throughout gestation, minimising complications like macrosomia, preterm birth, and neonatal hypoglycemia (63). Clinical practice guidelines from the Endocrine Society (2018) and the American Diabetes Association (2024) endorse lifestyle modification as first-line therapy, supported by glucose monitoring (64).

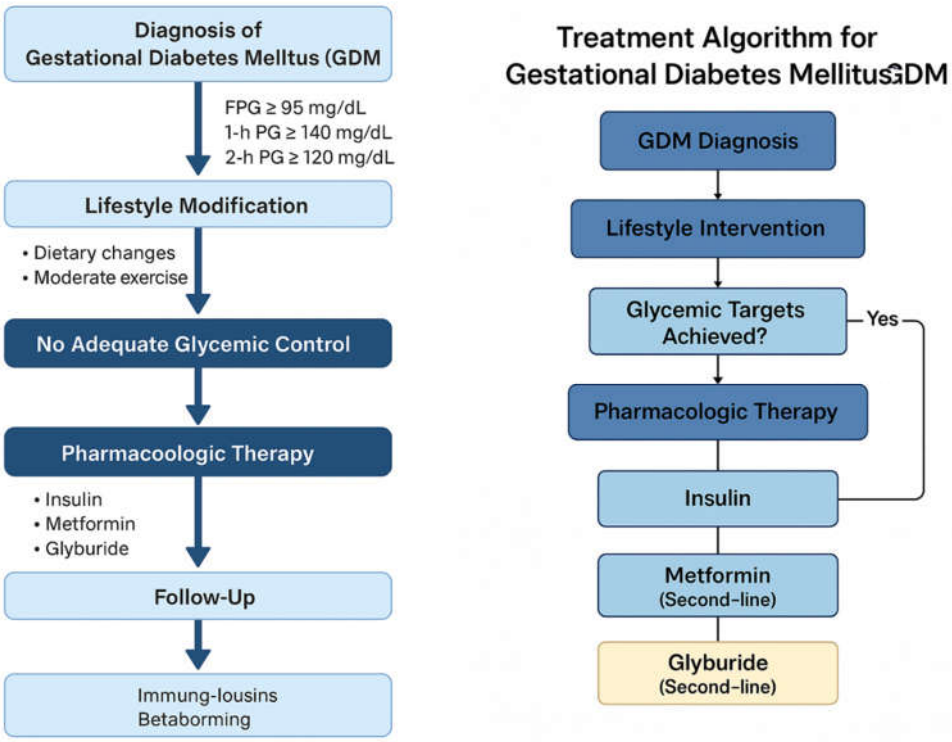

Figure 2: Current therapeutic approach for the management of Gestational diabetes

6.2.1 Lifestyle Interventions

Approximately 70–85% of GDM patients achieve glycemic targets through medical nutrition therapy (MNT) and physical activity alone (65). Dietary recommendations include carbohydrate-controlled meals with low glycemic index foods, frequent small meals, and emphasis on whole grains, vegetables, and lean proteins (66). Exercise has been shown to improve insulin sensitivity and reduce the need for pharmacological intervention (67).

However, individualised dietary counselling is often unavailable in LMICs, limiting MNT effectiveness. Moreover, compliance is hindered by cultural dietary norms, misconceptions about "eating for two," and food insecurity.

6.2.2 Pharmacological Therapy

When glycemic control is not achieved within 1–2 weeks of lifestyle intervention, pharmacotherapy is initiated. Insulin is the standard treatment of choice due to its efficacy, flexibility in dosing, and inability to cross the placenta. Short-acting (e.g., insulin aspart, lispro) and long-acting analogues (e.g., detemir) are commonly used (68). However, insulin therapy requires frequent blood glucose monitoring, poses a risk of maternal hypoglycemia, and may lead to excessive weight gain, particularly in women with obesity. Metformin, an oral biguanide that enhances peripheral insulin sensitivity, is increasingly used as a first-line agent. It crosses the placenta but has not demonstrated teratogenic effects (69). The MiG trial (2008) found similar neonatal outcomes with metformin compared to insulin, though metformin-treated women were more likely to require supplemental insulin (70,71). Long-term safety data, have raised concerns about higher adiposity in children exposed to metformin in utero, warranting further evaluation. Glyburide, a sulfonylurea, is still used in some settings but is associated with increased risk of neonatal hypoglycemia and large-for-gestational-age infants. As such, major guidelines now recommend glyburide only when insulin and metformin are not suitable or accessible (72).

6.2.3. *Shortcomings of Current Management Strategies*

Current treatment paradigms often prioritise glycemic normalisation over addressing the root pathophysiological mechanisms of GDM—insulin resistance, inflammation, and β-cell dysfunction. This approach may mask underlying metabolic dysfunction without preventing disease progression post-partum. Moreover, the focus on pregnancy-only management neglects the critical postpartum window, during which many women with GDM convert to overt type 2 diabetes (5,71). Follow-up data suggest that 30–70% of GDM patients develop T2DM within 5–10 years postpartum, yet postpartum screening rates remain abysmally low, especially in resource-constrained settings (73). Additionally, fetal risks such as epigenetic programming, increased adiposity, and future insulin resistance are not fully addressed by existing treatment models (40,74). This highlights the need for therapies that can modulate intrauterine metabolic programming, rather than just controlling blood glucose during gestation.

6.2.4. Emerging Strategies and Future Directions

As GDM is increasingly viewed as an early manifestation of broader metabolic dysfunction, the field is shifting toward precision medicine approaches aimed at early prediction, prevention, and targeted intervention (75,76).

6.2.4.1 Early Risk Stratification

Recent efforts have focused on identifying predictive biomarkers in the first trimester, including low sex hormone-binding globulin (SHBG), high-sensitivity C-reactive protein (hs-CRP), adiponectin, and specific microRNAs (e.g., miR-29a, miR-223). Integrating these markers with clinical factors (BMI, age, and PCOS history) may enable stratification into high- and low-risk categories by 12 weeks of gestation. Emerging tools, such as machine learning-based risk calculators and maternal metabolomics panels, are also under development to facilitate earlier diagnosis and intervention.

6.2.4.2 Novel Therapeutic Targets

Future pharmacologic interventions may go beyond glycemic control. Investigational strategies include GLP-1 receptor agonists (e.g., liraglutide), although these are contraindicated in pregnancy; these agents may be valuable in postpartum diabetes prevention. Probiotic and prebiotic supplementation is another approach that aims to restore gut microbial balance, improve insulin sensitivity, and reduce inflammatory cytokines(77–79). Moreover, Anti-inflammatory drugs that Target TNF-α and IL-6 signalling pathways are implicated in GDM-associated insulin resistance. New techniques like molecular docking could serve as an emerging tool for the identification of new therapeutic targets (80).

7. Management Strategies and Limitations

The management of gestational diabetes mellitus (GDM) focuses on achieving euglycemia to reduce the risk of adverse maternal and fetal outcomes. Standard treatment begins with lifestyle modifications, escalating to pharmacologic interventions when necessary. However, therapeutic approaches remain limited by individual variability in metabolic response, concerns regarding fetal safety, and lack of long-term data on newer therapies.

7.1. Lifestyle Interventions: First-Line Approach

Lifestyle modification is the cornerstone of GDM management and is effective in up to 70–85% of cases (81). Medical nutrition therapy (MNT), tailored to the patient's caloric needs, body mass index (BMI), and cultural food preferences, is central to this approach. Low-glycemic index diets, fibre-rich foods, and balanced macronutrient distribution (e.g., 40–50% carbohydrates, 20% protein, 30–35% fat) have been associated with improved glycemic control and reduced need for pharmacotherapy. Physical activity, especially moderate aerobic exercise like walking or swimming for at least 30 minutes daily, enhances insulin sensitivity and improves maternal glucose tolerance (82). A recent randomised controlled trial demonstrated that structured exercise interventions lowered fasting plasma glucose and postprandial spikes, delaying or eliminating the need for medication in over half of the participants (83). Despite the efficacy of these interventions, adherence remains a challenge, particularly in low-resource settings or among women with concurrent pregnancy-related complications.

7.2. Pharmacologic Therapies: Indications and Controversies

When lifestyle interventions fail to maintain glucose targets, typically fasting plasma glucose <95 mg/dL and 2-hour postprandial <125 mg/dL, pharmacological treatment is initiated (84). Insulin is the traditional gold standard due to its proven efficacy and inability to cross the placenta. However, its use requires frequent blood glucose monitoring, dose titration, and carries a higher risk of hypoglycemia and patient discomfort, particularly in low-literacy populations (68). Oral antihyperglycemics, notably metformin and glyburide, are increasingly used due to better compliance and cost-effectiveness. Metformin, which decreases hepatic gluconeogenesis and improves peripheral insulin sensitivity, is considered safe in the second and third trimesters. However, it crosses the placenta, and while short-term data have not shown teratogenicity, long-term outcomes, especially regarding childhood adiposity and metabolic syndrome, remain under investigation. Glyburide, a sulfonylurea, stimulates insulin secretion but also crosses the placenta and has been associated with neonatal hypoglycemia and macrosomia (85). Consequently, recent guidelines from ACOG and ADA recommend it as a second-line agent only when insulin or metformin is not feasible.

7.3. Emerging Therapies and Precision Approaches

Given the heterogeneity of GDM pathophysiology, there is growing interest in precision medicine matching treatment strategies with individual metabolic phenotypes and plant derived compumd based therapies (86–88). Emerging evidence suggests that maternal lipid profiles, insulin resistance severity, and inflammatory markers could predict responsiveness to specific

treatments. Probiotics and nutraceuticals are gaining attention as adjunct therapies. Probiotic strains such as Lactobacillus rhamnosus and Bifidobacterium lactis have shown promise in modulating gut microbiota, improving insulin sensitivity, and reducing inflammation. Additionally, nutraceuticals like myo-inositol, omega-3 fatty acids, and vitamin D have been investigated for their roles in glucose metabolism and β-cell function (89). A 2023 meta-analysis concluded that myo-inositol supplementation significantly lowered the incidence of GDM in high-risk women by enhancing insulin sensitivity and reducing fasting glucose levels (90). Despite encouraging results, the safety, standardisation, and dosage of these supplements remain poorly defined. Moreover, data from large, well-controlled trials assessing fetal outcomes and long-term efficacy are currently lacking.

7.4. Limitations and Unmet Needs

Major challenges in GDM management include suboptimal adherence to lifestyle protocols, variable pharmacological responses, and limited personalisation of therapy. There is also a lack of postpartum follow-up despite the well-documented risk of type 2 diabetes in women with prior GDM. Furthermore, treatment primarily targets hyperglycemia but often overlooks underlying mechanisms such as chronic inflammation, oxidative stress, and β-cell dysfunction. Although recent therapies are limited, making their novel formulations may serve an increased therapeutic effect (77,91,92).

7.5. Current Gaps and Future Directions

Despite mounting evidence on the long-term implications of GDM, postpartum follow-up rates remain dismally low. A 2023 systematic review found that less than 50% of women with prior GDM receive postpartum glucose screening or counselling (93,94). Barriers include a lack of standardised postpartum care protocols, fragmented healthcare systems, and poor awareness among both patients and healthcare providers. To address these gaps, integrated care models are urgently needed that bridge obstetric and primary care, emphasise continuity of care, and employ risk-based stratification for intensive follow-up. Recent pilot interventions, including digital health platforms and community-based support programs, have shown promise in enhancing postpartum engagement and adherence to lifestyle modifications.

Conclusion

Gestational diabetes mellitus (GDM) has emerged as a critical public health concern globally, with both immediate and long-term implications for maternal and offspring health. Its

increasing prevalence—particularly in low- and middle-income countries—is driven by urbanisation, dietary transitions, and demographic shifts, such as rising maternal age and obesity rates. Substantial regional and ethnic disparities reflect the interplay of genetic susceptibility, environmental exposures, and healthcare access. Although the IADPSG criteria have enhanced early detection, inconsistencies in diagnostic practices and debates around universal versus selective screening highlight persistent challenges in global implementation. This review underscores the complex pathophysiology of GDM, which extends beyond physiological insulin resistance of pregnancy to include β-cell dysfunction, chronic inflammation, oxidative stress, placental dysregulation, and gut microbiota alterations. These mechanisms help explain why GDM not only complicates pregnancy but also acts as a precursor to type 2 diabetes, cardiovascular disease, and metabolic syndrome in affected women. Standard management, including lifestyle modifications and pharmacologic therapies such as insulin and metformin, can mitigate short-term adverse outcomes. However, limitations remain due to variability in treatment response, underutilization of postpartum screening, and concerns regarding the long-term safety of certain medications on fetal development. Novel strategies such as probiotics, nutraceuticals, and individualised therapies offer promise but require further validation. The intergenerational consequences of GDM including increased risk of metabolic disorders in offspring—necessitate a shift toward integrated, life-course approaches. Long-term follow-up, early risk stratification, and culturally tailored preventive strategies are essential to reduce the cycle of metabolic disease transmission. Future efforts must focus on advancing mechanistic research, identifying predictive biomarkers, and applying precision medicine tools to improve outcomes. Simultaneously, addressing structural and socioeconomic barriers to care will be critical to translating scientific insights into meaningful health benefits across populations.

Author Contributions

Investigation, writing—original draft preparation, Khushi Patil, Bibi Muskan; writing—review and editing, Rashid Ansari; conceptualisation, Manoj Jograna; writing—review and editing, methodology, Muzammil Husain and Gaurav R Patil; conceptualisation, methodology, supervision, writing—review and editing, Nandkishor Talware. All authors have read and agreed to the published version of the manuscript.

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